PROSPECTIVE EVALUATION OF MUSCULOSKELETAL EVENTS IN PATIENTS OF CHRONIC MYELOID LEUKEMIA–CHRONIC PHASE TREATED WITH IMATINIB MESYLATE AND POSSIBLE CORRELATION WITH ELECTROLYTE IMBALANCES

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CERTIFICATE

This is to certify that this dissertation on **"Prospective evaluation of musculoskeletal events in patients of chronic myeloid leukemia –chronic phase treated with Imatinib mesylate AND possible correlation with electrolyte imbalances" ,** is a bonafide work done by Dr Peush Bajpai , in the Department of Medical Oncology , College of Oncological Sciences , Adyar , Chennai, under my overall supervision and guidance.

Place : Chennai
Date :

Dr T G Sagar MD , DM
Professor and Head
Department of Medical Oncology College of Oncological Sciences
Adyar , Chennai - 600020

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CONTENTS

ABSTRACT

Prospective evaluation of musculoskeletal events in patients of Chronic Myeloid Leukemia –Chronic Phase treated with Imatinib mesylate AND possible correlation with electrolyte imbalances

Introduction: Tyrosine Kinase inhibitors especially Imatinib have become the first choice of therapy in Chronic Myeloid Leukemia (CML).The adherence to therapy is an important factor required for achieving Molecular responses. Myalgia and Musculoskeltal pain are one of the common nonhematological toxicities affecting adherence.One of the most common hypothesis for this toxicity stated is Phosphate and calcium metabolism. We have done a prospective study to look into the incidence of Myalgia and Muscoloskeltal pain in our patients and also the abnormalities in serum electrolytes and also a possible correlation between the two.

Patients and Methods : We conducted a prospective observational study between January 2011- December 2012 where all new patients of CML without any relevant comorbids were included.Samples Of serum electrolytes(serum phosphate, sodium ,potassium and Calcium (along with Serum Albumin to check on ionized levels) were sent along with a urine spot sample for Creatinine and Phosphate to calculate serum phosphate at 0,3 and 6 th month.10 control samples were also sent to check for validation. Patients were followed up and hematological responses were recorded at each visit and history for any non hematological adverse effect especially myalgia was documented. Stastical analysis was done using paired t tests using SPSS software version 13

Results: 57 patients were included, median age 32y(4-65y),6 pediatric patients were included 92% achieved Complete hematological response at the end of first year. Myalgia and Musculoskeletal pain were the most common side effects(31%)next was hypopigmentation (8%). Grd 1 myalgia (68%) was most common. For serum electrolytes a decrease in trend from baseline values for serum Phosphate , Calcium and potassium was observed so also there was fractional increase in phosphate in urine. Correlation did not show any significant relationship between decrease in calcium and phosphate values and myalgia probably because of a small sample size. However decreasing potassium values at 3 rd month was having a close correlation (=0.07). Only 1 patient(3%) who had Grd 3 myalgia was non compliant.

Conclusions: Musculoskeletal pain and myalgia are one of the most common nonhematological toxicities on Imatinib although they tend to resolve they tend to be associated with relative hypokalemia and possibly relative hypophosphatemia and hypocalcemia .This probably warrant further study especially in the subset of pediatric and elderly patients where bone growth and bone mineral density might be affected adversely.

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal proliferative disorder of a pluripotent stem cell involving myeloid, erythroid, megakaryocytic, B, and sometimes T, lymphoid cells. CML is classified as a myeloproliferative disorder, but is distinguished from these diseases by specific cytogenetic and molecular abnormalities. CML is associated with the Philadelphia chromosome (Ph) involving a balanced translocation t(9;22) (q34, q11.2), and the related *break point cluster region-abelson*(bcr-abl) chimeric gene.[1]

Advances in understanding the disease pathophysiology and molecular genetics have yielded a wealth of information regarding CML. The efficacy of Imatinib mesylate therapy has radically changed the prognosis of CML. With Imatinib, the survival in CML has improved from a median of 3-6 years with hydroxyurea and interferon-alpha to an estimated 8-year survival rate of 80-90%.

Nearly 30% of patients are nonadherent to Imatinib (i.e. they have interruption of the drug because of their own and not because of physicians recommendation) this is as per a earlier study done at our centre. Nonadherence is because of various reasons and the chances of these patients to achieve a complete cytogenetic response(CCyR) becomes remote.[2]

Patients in nearly all regional cancer centres in India are getting Glivec through Glivec International Patient Assistance Program (GIPAP). It is one of the most comprehensive and far-reaching cancer access programs ever developed on a global scale.

Novartis designed Glivec International Patient Assitance Programme(GIPAP) to provide Glivec (Imatinib) free of cost to eligible patients in developing countries who meet specific medical and socio-economic guidelines. Through the Max Foundation, GIPAP also provides information and referral assistance to patients, their family members and caregivers.

Specifically: GIPAP helps patients who are properly diagnosed with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) patients and to patients with c-Kit (CD117) positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors (GISTs). GIPAP helps patients who are not insured, not reimbursed, cannot pay for treatment privately, and are in developing countries that have minimal reimbursement capabilities.

Considering this and that financial feasibility of second line Tyrosine kinase inhibitors is difficult it is important that our patients remain adherent to treatment. Some of the nonhematological toxicities of Imatinib cause intolerance and thus lead to non adherence too. CML patients who are in

chronic phase have the most common and worrisome nonhematological toxicity as musculskeletal pain and myalgia.

The 5 year follow up data of IRIS (International Randomized Study of interferon and STI517 trial) out of 551 patients on Imatinib who continued treatment, muscle cramps and myalgias were present in 38% and 21% of patients respectively; grade 3/ 4 cramps were in 1.3 % of patients and grade 3/ 4 of myalgia was found in 1.5% of patients . The cause of this has been unknown and the treatment advised for it is usually calcium supplementation, nonsteroidal anti inflammatory drugs (NSAIDs) and tonic water. Many hypotheses have been proposed in this regard and one of the closest contender is electrolyte imbalances namely of phosphate, calcium and possibly potassium. The two main theories behind this are.

1. Renal loss due to renal tubular dysfunction
2. Altered bone mineral metabolism

This study will look into the incidence of myalgia and musculoskeletal side effects of Imatinib and correlate these events with possible electrolyte imbalances in a newly diagnosed patient of CML who will be started on Imatinib.

The other objectives of this study are to look into non compliance due to this particular side effect and effect of NSAIDs and calcium supplementation in these patients.

AIM

Primary outcomes

1. To prospectively evaluate the incidence of musculoskeletal events (i.e. myalgia, bony pains & cramps) in CML chronic phase patients started on Imatinib.
2. Correlation of these events with electrolyte changes, namely serum calcium, serum phosphate and serum potassium**.**

Secondary outcomes

1. To estimate non-compliance because of these events.
2. Effect of analgesics and calcium supplementation in these patients.

REVIEW OF LITERATURE

Introduction

Chronic myeloid leukemia (CML) is the most common myeloproliferative disorder which has been defined by the presence of Philadelphia chromosome (9;22)(q34;q11) on karyotyping studies or the presence of bcr-abl fusion transcript which is in most cases a p210 variant. Philadelphia negative CML is a rare entity, the diagnosis of which is not easy as cryptic bcr-abl translocation can be present but can get missed during cytogenetic analysis. The myeloid cell proliferation involves the blood and reticuloendothelial compartments.[3,4]

Historical Perspective

It was John Hughes Benett, a pathologist who performed an autopsy of a patient who had presented to him with clinical picture of a massive spleen which was associated with leucocytosis He published his findings in the *Edinburgh Medical and Surgical Journal.* During the same period Rudolph Virchow saw a similar patient and unlike Benett who had concluded that his patient had died of the presence of "purulent matter" in the blood, Virchow coined the term "Weisses Blut", German for which is "Leukemie". It was in 1872 that Ernst Neumann described the origin of the disease to be in bone

marrow. Nearly 100 years later in 1960 the next important step happened which was the recognition of chromosome from the cells cultured from the blood of chronic granulocytic leukemia. This chromosome resembled a Y chromosome but was present in the karyotypes of women with this disease. This chromosome came to be known as Philadelphia chromosome, Rowley was able to further show in 1973 that it was a truncated version of chromosome 22 (termed as 22q-) and was a result of reciprocal translocation between chromosome 9 and 22. In 1970 Herbert Abelson had isolated a transforming gene from Moloney murine leukemia virus. In the early 1980s it was reported that the human counterpart of murine Abelson gene , now known as “abl “ was at human chromosome 9 but was translocated to the Ph chromosome in CML. This suggested the possibility that it would be the abl gene that would be the cause of CML. Groffen and colleagues reported the breakpoint on chromosome 22. This was clustered in 5.8Kilobase region on chromosome 22 that they termed as breakpoint cluster region (bcr).[5]

Research in the past two decades has established that it is the activity of bcr-abl tyrosine kinase which leads to transformation of hematopoietic cells into CML.

To determine whether P210 bcr/abl can induce chronic myelogenous leukemia, Daley et al conducted studies where murine bone marrow was

infected with a retrovirus encoding P210 bcr/abl and transplanted into irradiated syngeneic recipients. Transplant recipients developed a syndrome resembling myeloproliferative disorder which closely resembled the chronic phase of human chronic myelogenous leukemia.[6]

The *bcr-abl* + leukemias became the most thoroughly understood of human malignancies, in part because of the development of accurate animal models for these diseases.[7] The fact that it proved difficult to identify further downstream targets specific to the disease made bcr –abl most attractive therapeutic target.[8]

CML in Pre Imatinib Era:

In the pre Imatinib era as early as 1860 there were reports of use of Fowler's solution, and prior to radiotherapy, Arsenic was used in the treatment of high counts in a patient of CML.[9]

The first effective palliation was achieved by Radiotherapy which was usually directed to spleen; currently the role of radiotherapy is for Total Body Irridiation.[10]

Post World War II during the use of alkyaltors, Busulfan was introduced in the treatment of CML. It allowed longer periods of

hematological control but had severe and erratic myelosuppressive side effects.[5]

Hydroxyurea was introduced in 1972 and had a better toxicity profile than Busulfan and in a German /Swiss randomized study it came out as a superior alternative when it was compared with buslfan.[11]

It was the use of Interferon-α in CML that led one to ponder on the possibility of the idea of cytogenetic remission. Hematologic remissions have been noted in the majority of patients using IFNa-2a as a single agent and complete cytogenetic remissions (i.e., absence of any Ph+ metaphase by conventional cytogenetics) were noted in a minority of patients.[5,12]

The rate of cytogenetic response was higher in younger patients and in those with lower Sokal risk categories and those treated earlier. Although the degree of cytogenetic response improved over time, it was uncommon to observe cytogenetic responses with further treatment if no reductions in the percent of Philadelphia chromosome metaphases were seen during the first year of therapy. Because of the considerable side effects from interferon, many clinicians chose to stop interferon therapy if cytogenetic improvement had not been seen after approximately one year of treatment.[5]

An Italian trial showed improvement in survival figures when Ara –C was added to Interferon-α.[13]

The only curative option for CML was and remains Allogenic Stem cell transplant but in the era of tyrosine kinase inhibitors is usually a third line option, unless there happens to be a presence of T315I mutation or progression to accelerated and Blast phase.[14]

Development of bcr-abl tyrosine kinase inhibitor:

In 1992, Anafi and colleagues reported a tyrphostin, which was related to erbstatin, that inhibited the tyrosine kinase activity of bcr-abl and suggested that it might be possible to target abl associated leukemias with specific compounds. Subsequently, the tyrphostins AG568, AG957, and AG1112 were designed as the most specific compounds. Growth inhibition of the CML cell line occurred at micro molar concentrations by these compounds and was associated with inhibition of BCR-ABL tyrosine kinase activity. Although active in vitro, they have not been developed for clinical use.[15]

In the late 1980s, researchers at Ciba Geigy, started research on the identification of compounds with inhibitory activity against protein kinases. In one project focusing on protein kinase C (PKC) as a target, a 2-phenylaminopyrimidine derivative was identified as a parent compound. This compound had low potency and poor specificity, inhibiting both serine/threonine and tyrosine kinases, but it was the lead molecule and

following this, with an array of permutations and combinations, several molecules came into picture and eventually came STI571, now called Imatinib Mesylate, which was highly selective for bcr-abl.[8]

Mechanism of action of Imatinib

Imatinib mesylate (Gleevec, or STI 571) binds to the ATP-binding site of the brc-abl oncoprotein and prevents transfer of phosphate from ATP to the second messenger. Hence, it prevents further downstream signals which lead to cell growth arrest and eventually apoptosis due to lack of growth signals.

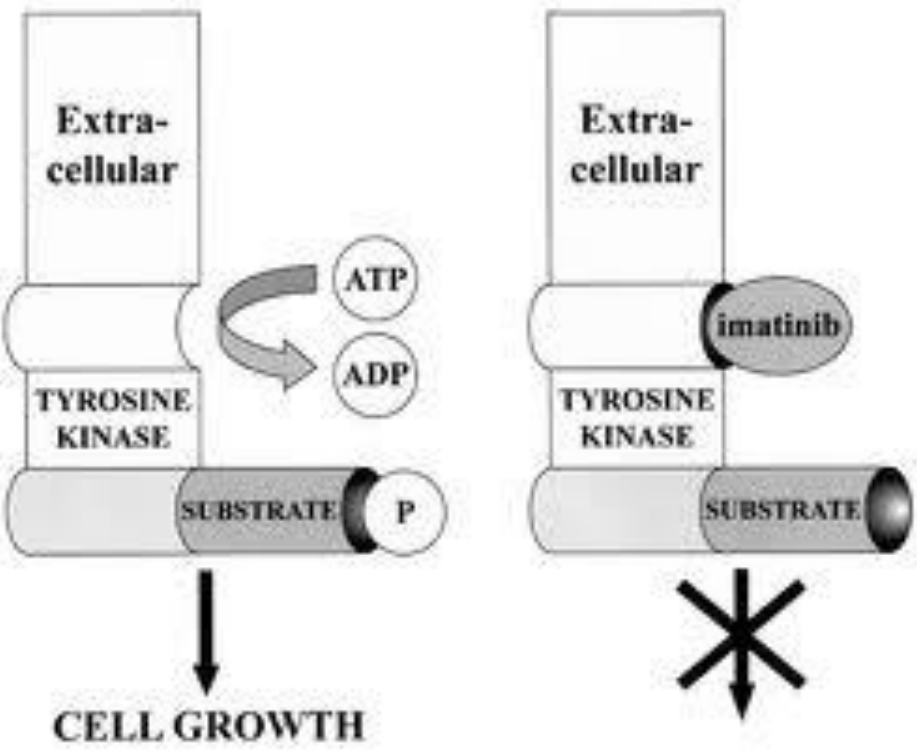


Figure 1: Mechanism of action of Imatinib[16]

Though designed to target bcr-abl specifically, Imatinib targeted many off target kinases; at a Cmax of 4.6μM it inhibits, apart from bcr-abl, the following:

- collagen induced discoiddin domain receptor -1,
- PDGFR-α & β
- C-kit
- the macrophage colony stimulating factor(M-CSF) receptor and c-fms.
- nontyrosine kinase targets include NAD(P)H :quinine oxidoreductase 2 and some family members of carbonic anhydrase (CA) family of metalloproteineases.

These *off target signaling* can lead to unwanted side effects and though some of these inhibitory mechanisms have come in use in treatment of other malignant conditions e.g. GIST, certain side effects are now being explained on the basis of these inhibitory actions, such as that of inhibition of bone remodeling.[17]

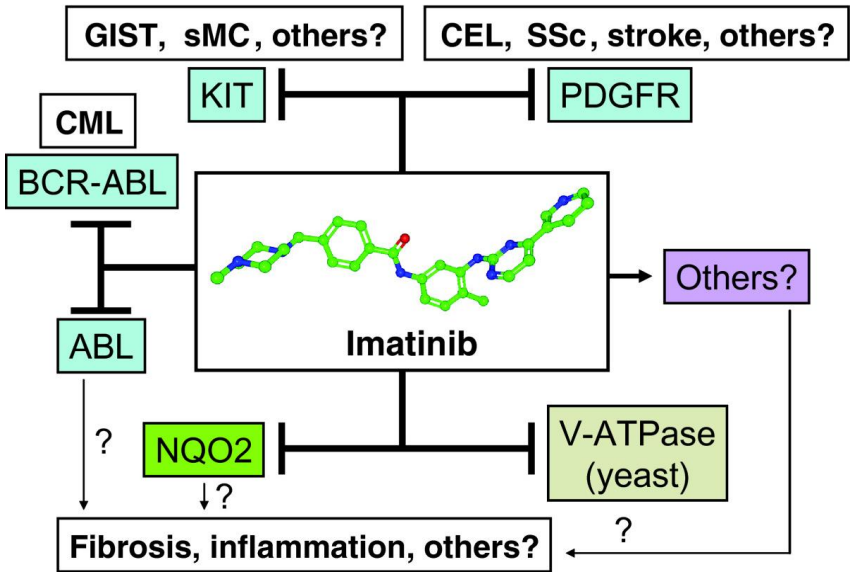


Figure 2 Nonspecificity of Imatinib :inhibitory actions apart from bcr-abl[18]

Imatinib era in CML: Current status of Imatinib as frontline therapy

Imatinib has now been the first line therapy in the management of CML for nearly a decade. In phase 1 trial by Duker et al, 83 patients who failed interferon therapy were given Imatinib in escalating doses ranging from 25 mg -1000 mg. Above a dose of 300 mg nearly 31% patients achieved cytogenetic response. This lead to important finding of a oral medication which had shown remarkable efficacy with lesser toxicity.[19]

Phase 2 trials began in late 1999 and the drug showed efficacy in all the three phases which led to its approval by the Food and Drug administration (FDA) in CML resistant to interferon therapy and in the advanced phase of disease.[8]

Phase 3 trial was an open labelled multicentre trial, published in 2003 in *New England journal of medicine,* and was a comparison of Imatinib and Interferon α with low dose Ara-C. Crossover from one arm to the other was allowed. The results published in 2003 were a 19 month follow up which revealed a major cytogenetic response (MCyR) in nearly 87% of patients (i.e. those who had 0-35% of cells which had metaphase positivity and the rates of complete cytogenetic response (CCyR) were 87% in contrast to the other arm of Interferon and low dose Ara-C where CCyR was just 14.5%.[20]

At end of 8 years, 304 (55%) patients were on Imatinib. 45% had discontinued treatment due to adverse effects and safety (6%), unsatisfactory therapeutic outcome (16%), death (3%), SCT (3%) and other reasons amongst which were lack of consent, withdrawal or miscellaneous . No safety issues were identified in a long term analysis of serious adverse effects. The results were as follows: Estimated EFS at 8 year was 81% and freedom from progression to AP/BC was 92%. Estimated OS was 85% at 8 year, and 93% when only CML-related deaths and those prior to SCT were considered. Three events occurred in year 8: 1 progression to AP/BC and 2 deaths unrelated to CML (chronic obstructive pulmonary disease; pneumonia aspiration. The annual rates of progression to AP/BC in year 4 to 8 after initiation of therapy were 0.9%, 0.5%, 0%, 0%, & 0.4%, respectively. Only 15 (3%) patients who

achieved complete cytogenetic response (CCyR) progressed to AP/BC, all but one within two years of achieving CCyR[21].

Monitoring responses on Imatinib therapy[14]

Table 1. Responses on Imatinib: defining complete hematological response(CHR), cytogenetic responses and molecular responses

Definitions of Hematologic, Cytogenetic, and Molecular Response	
RESPONSE BY TYPE	**DEFINITIONS**
Hematologic Responses Complete Hematological Response (CHR)	WBC < 10 X 10^9/L Basophils _ 5% No myelocytes, promyelocytes, myeloblasts in the differential Platelet count <450 X 10^9/L Spleen nonpalpable
Cytogenetic Responses Complete (CCgR) Partial (PCgR) Minor (mCgR) Minimal (minCgR) None (noCgR)	 No Ph + metaphases 1% to 35% Ph+ metaphases 36% to 65% Ph+ metaphases 66% to 95% Ph+ metaphases 95% Ph+metaphases
Molecular Responses Complete (CMolR) by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10^4) Major (MMolR)	 Undetectable *BCR-ABL* mRNA transcripts Ratio of *BCR-ABL* to *ABL* (or other housekeeping genes) < 0.1% on the

	international scale

Table 2. Monitoring responses: time frames

Response	Description of monitoring
Hematologic	At diagnosis, then every 15 days until CHR has been achieved and confirmed, then at least every 3 months or as required
Cytogenetic	At diagnosis, at 3 months, and at 6 months; then every 6 months until a CCgR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured; always for occurrences of treatment failure (primary or secondary resistance), and for occurrences of unexplained anemia, leukopenia, or thrombocytopenia
Molecular by RT –PCR	Every 3 months until MMolR has been achieved and confirmed, then at least every 6 months
Molecular by Mutational analysis	In occurrences of suboptimal response or failure; always required before changing to other TKIs or other therapies

Duration of treatment with Imatinib[22]

In a prospective, multicentre, non-randomised Stop Imatinib (STIM) study, Imatinib treatment (of >2 years duration) was discontinued in patients with CML who were aged 18 years and older and in CMR (>5-log reduction in BCR-ABL and ABL levels and undetectable transcripts on quantitative RT-PCR). 100 patients were enrolled. Median follow-up was 17 months (range 1-30), and 69 patients had at least 12 months follow-up (median 24 months, range 13-30). 42 (61%) of these 69 patients relapsed (40 before 6 months, one patient at month 7, and one at month 19). At 12 months, the probability of persistent CMR for these 69 patients was 41% (95% CI 29-52). All patients who relapsed responded to reintroduction of Imatinib: 16 of the 42 patients who relapsed showed decreases in their BCR-ABL levels, and 26 achieved CMR that was sustained after Imatinib rechallenge. This reveals that patients have to be continued on Imatinib lifelong unless they undergo Allogenic transplant and do not have any residual disease detected post same.

Imatinib use and concerns with Musculoskeletal events-

The most common nonhematologic adverse events with a suspected relationship to Imatinib were nausea, muscle cramps, fluid retention, diarrhea, musculoskeletal pain, fatigue, and skin rashes.

Only a minority of patients experienced grade 3/4 toxicity. The incidence of some specific adverse events was also different according to the stage of disease. For example, vomiting and fluid retention were more common in patients with advanced-phase disease, whereas musculoskeletal symptoms and weight gain were more prevalent in patients in the chronic phase.[23]

The importance of Muscloskeletal and joint pains as nonhematological toxicity:

In a study by David Marin et al, the daily intake of Imatinib is of utmost importance in patients who are in cytogenetic remission in order to achieve a molecular response. In his study he found the major cause of non-adherence in younger patients to be myalgias and musculoskeletal pain. The median age for patients with an adherence rate< 90% was 43.8 years compared to 53.8 years for patients with a rate greater than 90% ($P < .004$). They found significantly lower adherence rates in patients with muscle cramps, and bone or joint pains.[24]

Musculoskeletal complaints are a common side effect of Imatinib and are manifested as muscle cramps and bone pain. The muscle cramps occur mainly in the hands, feet, calves, and thighs. The pattern, frequency, and severity of cramps are usually constant over time, and they may resemble titanic contractions. Some patients relate cramps to exertion or describe night time occurrence. Bone pain and arthralgias have been reported by 20% to 40% of patients. Their onset tends to be in the first month of therapy, and they frequently abate after a few months. The symptoms most frequently affect the femurs, tibias, hips, and knees. Bone or joint pain can be severe and disabling and may be strikingly asymmetric. In some cases, imaging studies were done but failed to detect abnormalities.[23]

Electrolyte imbalances associated with Imatinib and their association with myalgia [25]

HYPOPHOSPHATEMIA i.e serum Phosphate level< 2.7mg/dl (2.7mg/dl-4.5 mg/dl) :

This is the most common electrolyte imbalance associated with Imatinib. The most common medical causes of hypophosphatemia described in literature are -

- Increased renal loss due to tubular defects
- Drugs which cause phosphaturia,
- Hyperparathyroidism,
- Vitamin D deficiency

The clinical manifestations of mild hypophosphatemia include myalgias, weakness, anorexia. Chronic severe depletion may be manifested by pain in muscles and bones.

The phosphate levels should be monitored in a fasting state as there is an impact on serum levels of phosphate done on a post prandial sample. Spot urine value of phosphate > 20mg/dl suggests phosphate loss in urine. Phosphate excretion can be measured either from a 24-hour urine collection or by calculation of the fractional excretion of filtered phosphate (FEPO4) from a random urine specimen. The formula used to make the latter calculation is the same as that for the fractional excretion of sodium: FEPO4 = [URINE PO4 x PLASMA Cr x 100] ÷ [PLASMA PO4 x URINE Cr] where U and P refer to the urine and plasma concentrations of phosphate (PO4) and creatinine(Cr).

Low phosphate excretion — Daily phosphate excretion should be less than 100 mg and the fractional excretion of phosphate should be well below five percent (normal value is five to 20 percent) if the kidney is responding normally and renal phosphate wasting is not the cause of the hypophosphatemia.

HYPOCALCEMIA i.e serum calcium levels < 8.4mg/dl (normal levels - 8.4-10.2mg/dl)

This is the second most common abnormality which was detected in patients on Imatinib, Hypocalcemia increases excitation of nerve and muscle cells, primarily affecting the neuromuscular and cardiovascular systems.

Extensive spasm of skeletal muscle causes cramps and tetany. In true hypocalcemia serum ionized calcium is taken into account. Some common medical causes stated are

- Decrease intake or absorption- Malabsorption, small bowel bypass
- Increased loss- Diuretic, alcohol abuse
- Decreased resorption from bone- use of zolendronic acid
- Endocrine disorders-Hyoparathyroidism

HYPOKALEMIA i.e serum levels<3.5mg/dl (normal levels 3.5-5.2mg/dl)–

Described only in case reports in patients who are on Imatinib, this is also a possible cause of myalgia and muscle spasms but does not cause arthralgia /bony pains

- Decreased intake
- Renal Potassium loss- due to increase aldosterone levels, Fanconi syndrome, diuretics
- Loss through extrarenal routes- villous adenomas, Zollinger Ellison syndrome (ZES), laxative abuse

Musculoskeletal pain/ myalgia inpatients on Imatinib and possible association with electrolyte imbalances- existing literature

The treatment which has been advised by NCCN and other literature evidence states that calcium supplementation is an important treatment aspect in the management of musculoskeletal pain along with fluids supplementation.

The cause of this pain has not been quite clear, however there have been reports that hypocalcemia and hypophosphatemia might be associated with these symptoms.

- In a case series reported by Zekri et al, they found a sustained fall of calcium levels in their patients.[26] Prior to this study they had studied an index case where they had found a similar trend of fall and there was associated myalgia and musculoskeletal symptoms in that patient. The probable hypothesis given for hypocalcemia by them was that

1. Imatinib was acting on the c-kit receptor of the renal tubule and causing hypocalcemia
2. Or Imatinib might be causing nonspecific inhibition of calcium channels in tubule which might be leading to same

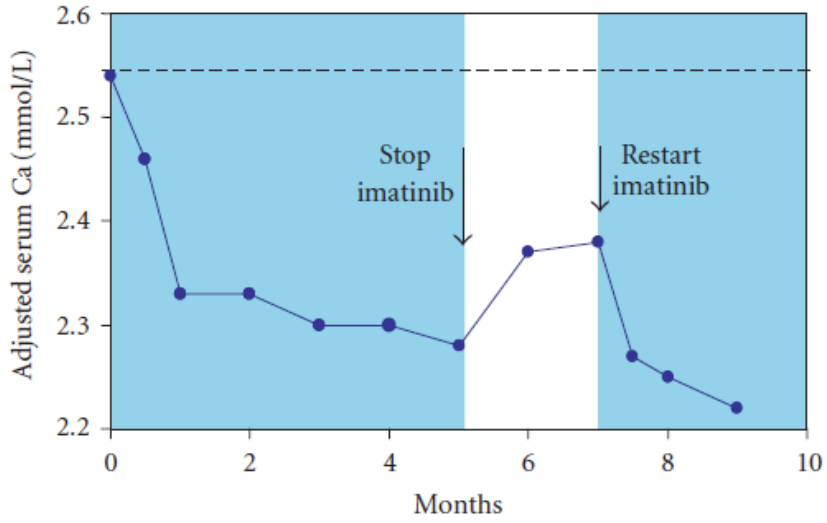


Figure 3 Changes in adjusted serum calcium levels in the index case : courtsey Zekri et al[26]

- The renal tubule affection also has been described by Rodrigo Azevedo de Oliveira[27] et al where they described a patient who had acute tubular necrosis which was related to Imatinib and this eventually led to electrolyte imbalances. The hypothesis given by them was that Imatinib inhibited PDGFR –α in proximal tubules and c-kit receptor in distal tubules which led to hypophospahatemia and hypocalcemia respectively, but the case reported by them did not have any musculoskeletal symptoms and was on Imatinib for past 4 years.

- Likewise another case report by Helene Francois et al[28] showed development of partial Fanconi syndrome with patient having hypophosphatemia, hypouricemia and glycosuria. The renal biopsy done showed vacuolations in the proximal renal tubule. This patient also developed myalgia when the treatment was started. They hypothesized that PDGF pathway inhibition which is responsible for regeneration of proximal renal tubule is inhibited by Imatinib hence it could cause Fanconi syndrome.

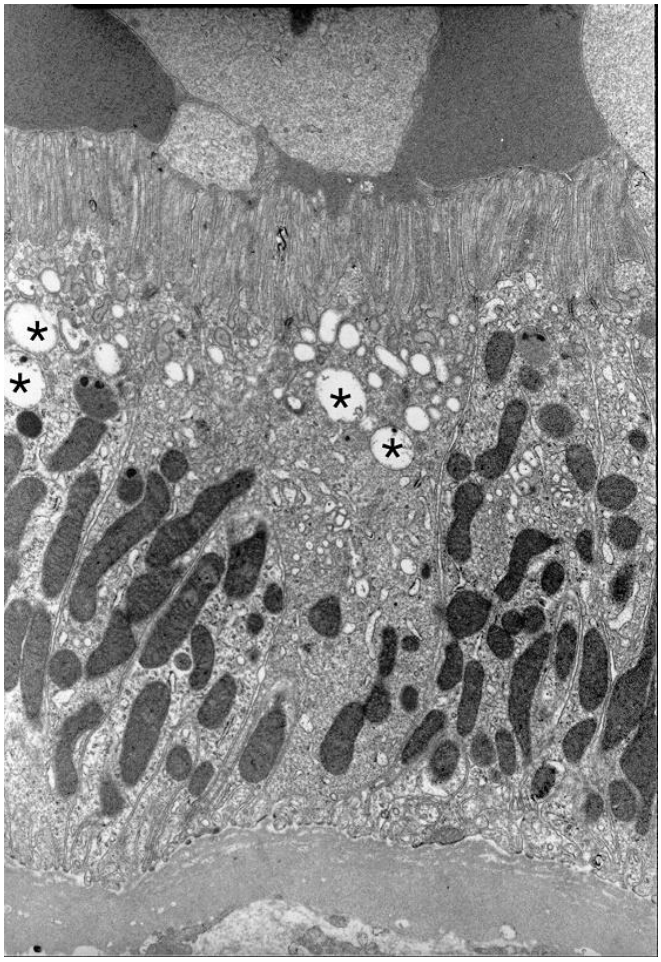


Figure 4: Electronmicrograph showing vacuolation in proximal renal tubule[28]

- The recent research by Berman[29] et al highlighted the possibility of effect of Imatinib causing hypophosphatemia as a part of effect of Imatinib on bone metabolism. They have hypothesized that the drug acts on bone by inhibition of osteoclast function directly by inhibiting PDGFβ and indirectly by inhibiting PDGFα receptor present on osteoblasts. This eventually leads to decreased bone remodeling and thus decreased calcium and phosphate in the

serum and since deceased ionized calcium can induce hyperparathyroidism, this eventually leads to increased phosphate excretion and decreased calcium excretion.

Their study was based on a set of 16 patients who they found on retrospective analysis to be having low serum phosphate and these patients were on Imatinib either for CML chronic phase or for Gastrointestinal stromal tumor (GIST). They found that those with low phosphate levels had increased levels of PTH (parathyroid hormone), low to normal levels of calcium and high levels of phosphate being excreted in urine (spot test). The article published by them in NEJM in 2006 May was followed by a Letter to Editor which was written by Dr Samantha Owen from Novartis, which stated that although hypophosphatemia of Grade 2 or above was mentioned in nearly 50% of the patients (Common Toxicity Criterion), it was reported only in 3% of patients eventually as an adverse event. So, probably, low Grade of hypophosphatemia went under reported for which Novartis advised the need to continue monitoring phosphate levels in patients who are on Imatinib, as a possible effect on bone mineral metabolism is possible.[30]

The flaws in the study accepted by the author were also stated in another letter to the editor which mentioned them as follows:

1. No measurement of baseline phosphate levels uniformly in all the patients studied.
2. Calcium levels were not corrected for albumin levels in the study
3. Blood sampling done was not standardized with respect to time and fasting status.
4. Small number of patients.

The authors had earlier in the original article mentioned their reasons for the delayed sampling of phosphate and also explained that despite the expectation that postprandial phosphate levels will be high they still got a low levels of serum phosphate levels and also the PTH levels were high which confirmed their hypothesis.

- In the same edition of the journal Joensuu and Reichardt[31] present data on 11 patients in which they did a longitudinal follow up of 11 patients, of which, 9 patients (82%) had a lower mean levels of plasma phosphate levels and these patients were on Imatinib 400mg which was being given as adjuvant treatment for GIST. They found that the plasma phosphate levels returned to normal after the discontinuation of the drug and that none of the patient had any skeletal event documented.

- Another similar study by Susannah O'Sullivan et al planned a longer follow up with similar parameters as studied by Berman et al based on a

similar hypothesis, with the objective of studying the biochemical and skeletal effects of Imatinib with long term treatment.[32] Their follow up period was 2 years, the study design was prospective and all patients were of CML on 400 mg of Imatinib. They had 9 patients in their study and they concluded similarly that there was decrease in calcium and phosphate levels starting at their first follow up period of 3 months. It was also documented that at a period of 18 months, these levels, although lower than baseline at 18 months, were not quite different when compared at 6 monthly follow up. They also demonstrated, like Berman et al, mild increase in PTH levels compared with baseline but this again plateaued at three months. Also studied were the markers of bone resorption which showed an initial increase followed by a decrease in levels, i.e., there was a biphasic effect. They also found an increase in bone mineral density at the end of two years. They also concluded that there was no evidence for phosphaturia due to Fanconi syndrome causing depletion of phosphate levels as they had monitored glucose and amino acids in the urine at 0 and 3 months respectively.

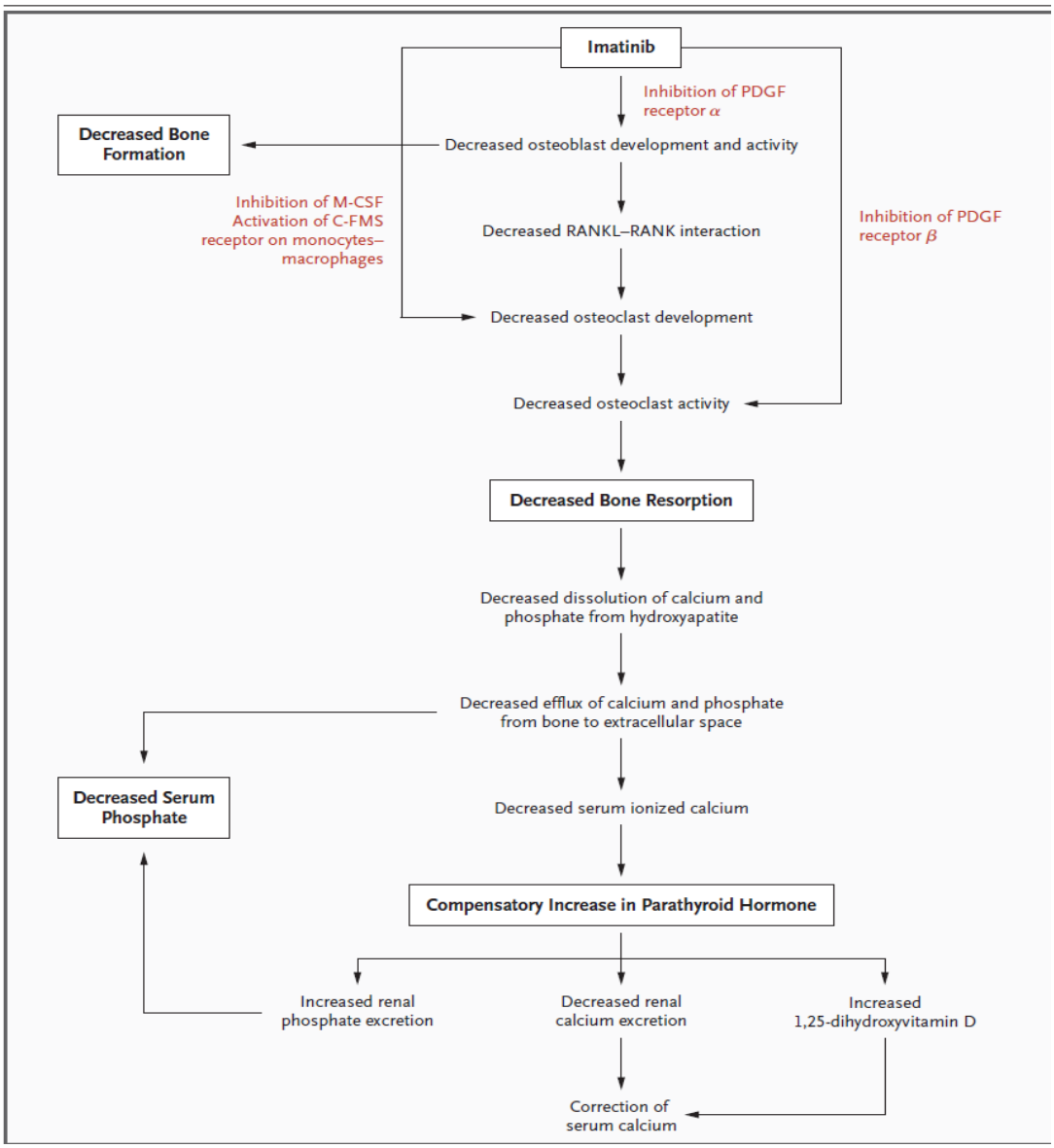


Figure 5: Hypothesis of how the sequence of events lead to hypophosphatemia in patients who are on Imatinib by Berman et al[29]

- Kate Vandyke et al[17] in a review article supported the theory of Berman et al and explained that the receptor required for differentiation of osteoblast was PDGFR which was inhibited by Imatinib and thus Imatinib decreases their proliferation but increases their activity. For osteoclasts, which are actually derived from monocyte/macrophage lineage, the effect of Imatinib was on c-fms receptor, c-kit receptor and a non specific action was on carbonic anhydrase II enzyme which is actually responsible for resorption of bone and is secreted by the resoptive surface of osteoclasts. They concluded that although the long term effect of Imatinib was not known, it could cause decreased bone turnover as caused by microfractures by prolonged use of bisphosphonates.

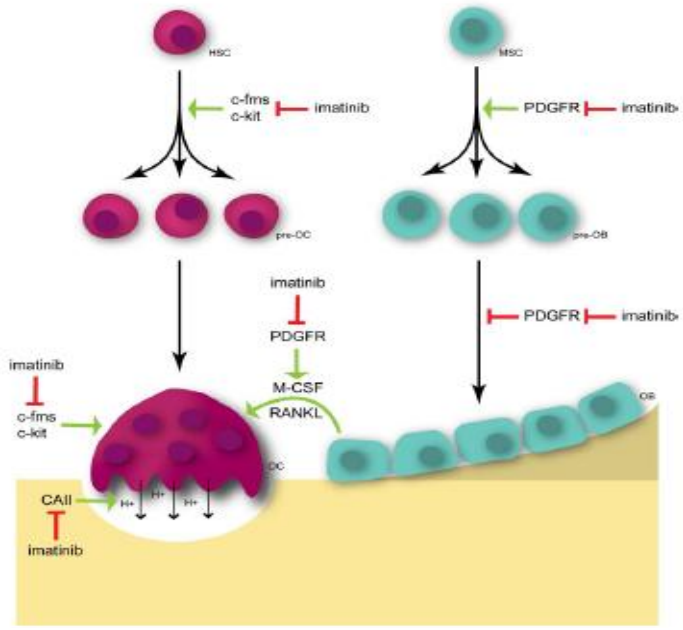


Figure 6 Inhibition of PDGFR in osteoblast precursor and c-fms and c-kit in osteoclast precursors by Imatinib[17]

- The largest series available till date, by S.Osorio et al, is a retrospective analysis of 36 patients.[32] The aim of the study was to find the metabolic cause of cramps and musculoskeletal symptoms. They studied several parameters of phosphate and calcium imbalances along with renal functions in 36 patients who have been on Imatinib. Most of these patients had been on Imatinib for a median period of nearly four years. These patients were being followed up 3 monthly and the investigations done revealed hypophosphatemia over time, and a decrease in trend of calcium levels but no definite hypocalcemia. They did not find any correlation that would suggest secondary hyperparathyroidism as the cause of hyperphosphatemia, and since they found that there was lesser tubular reabsorption rates, they hypothesized renal tubule c-kit receptor being inhibited by Imatinib which causes decreased phosphate reabsorption. They also found in their study a correlation between hypophosphatemia and better cytogenetic responses in their patients.

Impact of hypophosphatemia in pediatric patients on Imatinib[33]

Imatinib was licensed for the use in children by the FDA in 2003 for CML. Doses for children are different form adults. Doses of 260 to 340 mg/m^2 give drug exposures similar to the 400 to 600 mg adult dosage levels; therefore, the starting dose in children should be 300 mg/m^2 orally once daily (maximum absolute dose, 400 mg). The recommended pediatric doses for CML-AP are 400 mg/m^2 daily (maximum absolute dose, 600 mg) and for CML-BP 500 mg/m^2 daily (maximum absolute dose, 800 mg).

There is increasing evidence now that hypophosphatemia in patients on Imatinib is involved in dysregulated bone metabolism. There have been studies which have shown that when given in prepubertal age group it can cause decrease in longitudinal growth of the child because of possibly premature closure of growth plate. Hence it becomes important to regularly monitor growth of the child along with the desired cytogenetic responses at appropriate time frames so that an alternative treatment strategy can be worked out when needed for these patients, which is usually allogenic transplant.

Options for patients who develop musculoskeletal pain /myalgia on Imatinib-"INTOLERANCE"[14,34]

There is enough data now that there is minimal cross intolerance of second line Tyrosine kinase inhibitors when given in case of intolerance to Imatinib. With reference to myalgia there is less of it associated with second generation agents as these are more specific and have more affinity towards bcr-abl as compared to Imatinib. Any grade myalgia reported with nilotinib at a dose of 300mg BD was 7% and 6% in those who received 400 mg BD. Similarly, for Dasatinib, myalgia of any grade was present in 6% of patients. It is also stated that the hypophosphatemia caused by both these drugs is significant.

Below is a table with comparative results from three drugs

Table 3

AE	Imatinib	Nilotinib	Dasatinib
Fluid retention	+++ **mainly** low grade	(+)	(+)
Nausea, diarrhea, vomiting	++	(+)	(+)
Pleural effusion	-	-	++
Myalgia	+++	(+)	(+)
QTc prolongation	+	+	+
ALAT/ASAT/bilirubin increase	+	++	+
Lipase/ amylase increase	+	++ (should not be given in case of preexisting pancreatitis)	+
Glucose levels	Hypoglycemia	Hyperglycemia	Constant
Hypophosphatemia	++	+	+
Rash, pruritis	+	++	(+)
Anemia	+	+	+
Neutropenia	++	+	+
Thrombocytopenia	+	+	++

With the definition of Imatinib intolerance getting more precise *it is important to switch over to second generation drug so that adherence to the drug can be maintained.*

The intolerance to Imatinib is defined as following

(1) any life-threatening grade 4 nonhematological toxicity

(2) any grade 3/4 nonhematological toxicity that has recurred despite dose reduction

(3) any grade 2 nonhematological toxicity that persists for more than a month despite optimal supportive measures

(4) grade 3-4 hematological toxicity that is unresponsive to supportive measures and would require dose reductions below the accepted minimal effective dose.

This study is relevant because there is limited information on this particular and important side effect of Imatinib. The available prospective studies are very few, with only small number of patients, and there is no published literature from the Indian subcontinent on the subject.

PATIENTS AND METHODS

Study design This is a Prospective Observational study

Inclusion criterion

Between the period of January 2011-December 2012 all new cases of chronic myeloid leukemia who were to be started on Imatinib in our hospital and did not have previous exposure to the drug prior were included.

Exclusion criterion:

– Patients presenting with baseline musculoskeletal disease as Rheumatoid Arthritis,SLE.

– Patients with deranged renal function: Cr>1.5mg/dl.

– Patients on drugs other than Imatinib which are known to produce myalgia eg. Statins , HAART therapy.

– Prior to sampling for electrolytes, acute causes known to cause electrolyte imbalances eg. diarrhea, emesis, poorly controlled diabetes, tumor lysis were to be excluded.

Methods

- We at Cancer Institute (WIA) have a CML outpatient clinic on Thursday where Chronic Myeloid Leukemia patients are followed up.

- History of the patient was recorded especially with respect to any baseline history of myalgia and musculoskeletal event. After checking that patient is not in tumor lysis and also not any other medication known to cause myalgias, patient's baseline (prior to starting Imatinib) blood sample was collected preferably during fasting period or otherwise prior to 11 AM for analysis of serum electrolyte panel which includes Serum Phosphorous, Serum Calcium, Serum Potassium and Serum Sodium also Serum Creatinine along with Serum Albumin (for calculation of ionized serum calcium levels). This was collected along with a spot urine sample for analyzing spot urine creatinine and spot urine Phosphorus. Likewise, after starting Imatinib the date of starting the drug was noted and these patients were followed up with similar sampling done at 3 months and 6 months.
- Nonhematological toxicity was recorded, and if myalgia /musculoskeletal pain was present, detailed history was noted. Grading for myalgia/musculoskeletal event was done as per Common Toxicity Criterion version 2.0.

- Compliance issues related to any cause were noted and also if it was related to musculoskeletal event was recorded. This was highly dependent on patient's history and any nonadherence to the drug which exceeded more than 1 week was considered significant and recorded.[2]

- At follow up of 3 months the patients were evaluated whether they achieved Complete hematological response or not. Due to logistical aspects monitoring by FISH (Fluoroscent in situ Hybridization) was done usually at end of 1 year.

- In case of patient developing myalgia and Musculoskeletal pain, patient was started on NSAID's for a period of 5 days and Calcium tablets were also prescribed 500mg daily once.

- Response of myalgia and musculoskeletal event was recorded on next visit.
- Samples of 10 controls Were also sent for comparision and validation.

Grade

Table 4 : CTC response criterion used for grading

Adverse event	0	1	2	3	4
Myalgia (muscle pain)	None	Mild pain not interfering with function	Moderate pain or analgesics interfering with function, but not interfering with activities of daily living	Severe pain or analgesics severly interfering with activites of daily living	Disabling

- Measurement of the following and serum creatinine and spot urine tests were done at biochemistry lab at our institute. The following blood and spot urine tests were done

1. Serum Sodium (Na^+)
2. Serum Potassium (K^+)
3. Serum Phosphate (PO_4)
4. Serum Calcium along with Serum albumin
5. Serum creatinine
6. Spot urine Phosphate
7. Spot urine Creatinine

Serum and urine electrolyte measurements were done with automated analyzer A-25(BIOSYSTEMS©)

Figure 5: Automated Analyzer A-25(BIOSYSTEMS©)

- **Formulas used**

1. Fractional excretion of phosphate in urine

FEPO4 = [URINE PO4 x PLASMA Cr x 100] ÷ [PLASMA PO4 x URINE Cr].

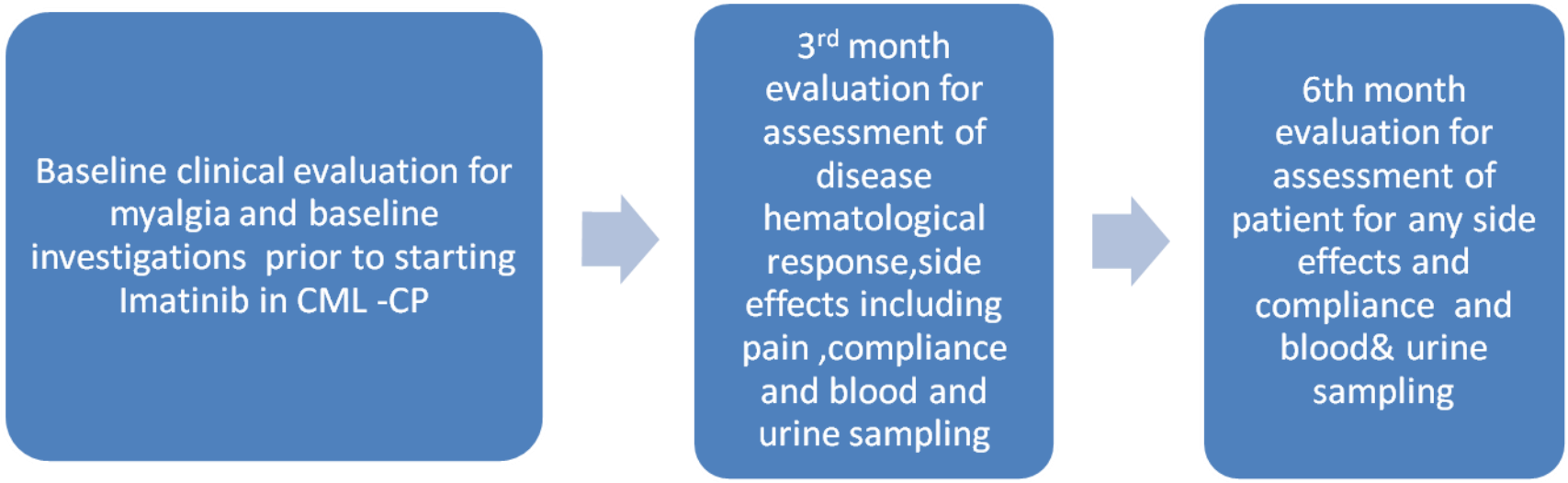
NORMAL VALUES: between 5-20%

2. Corrected Calcium = [0.8 * (Normal Albumin - Pt's Albumin)] +Serum Calcium.

- **Statistical methods used for analysis** :

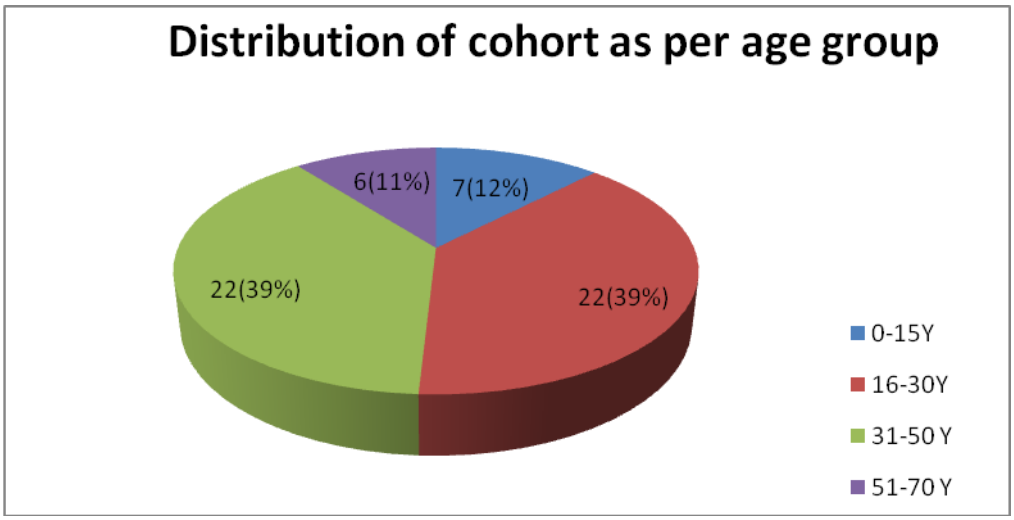
The descriptive statistics of the variables studies were represented as two way tables. The categorical factors were represented by the number and frequency (%) of cases. The continuous variables were represented by measures of central frequency (like mean, median) and deviation (standard deviation and range). For variables measured on a continuous scale, when testing for two groups, Student “t” test was used to test for statistical significance in the differences of the two means. Analysis was carried out using SPSS version 13 software.

Flowchart of Patient Follow Up:



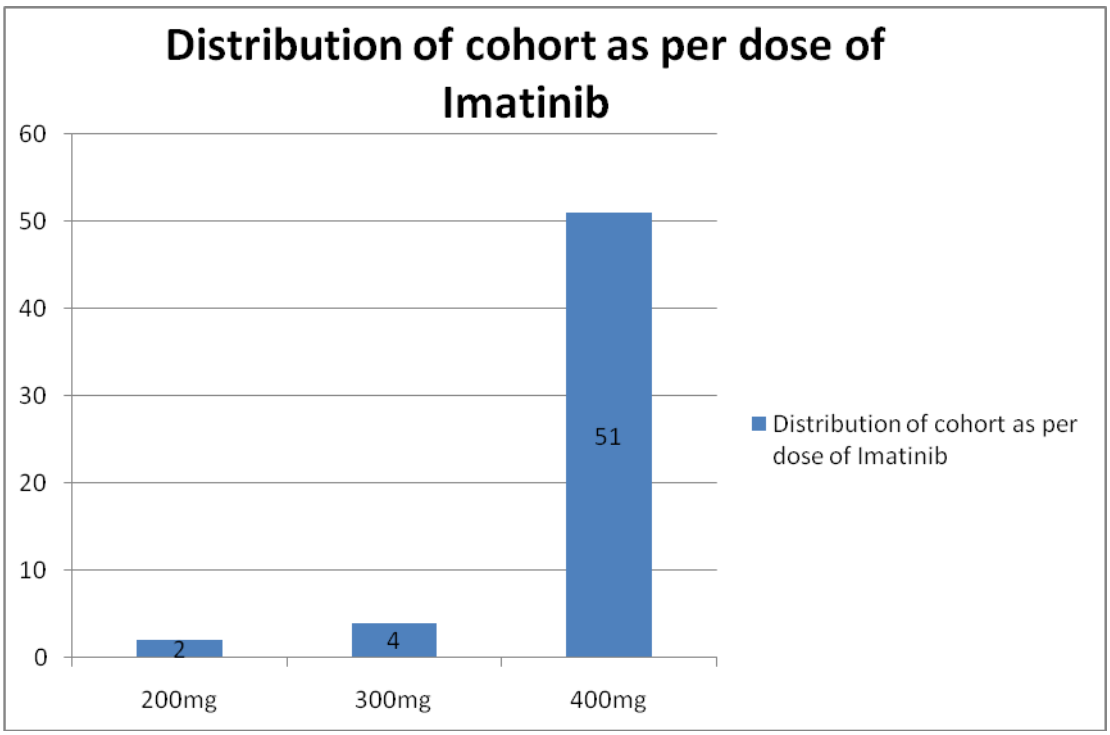
RESULTS

Fifty seven patients were included in the study over the year 2011. Median age was 32 years (4-65years) of which there were 44 males and 15 females with a male : female ratio of 1.94:1. Of these, 2 patients were not taken for the study as 1 patient after baseline investigations was revealed to be on antipsychotic medications and diuretics and another patient progressed within 3 months of starting Imatinib into blast crisis. The age distribution is shown in the pie chart below.



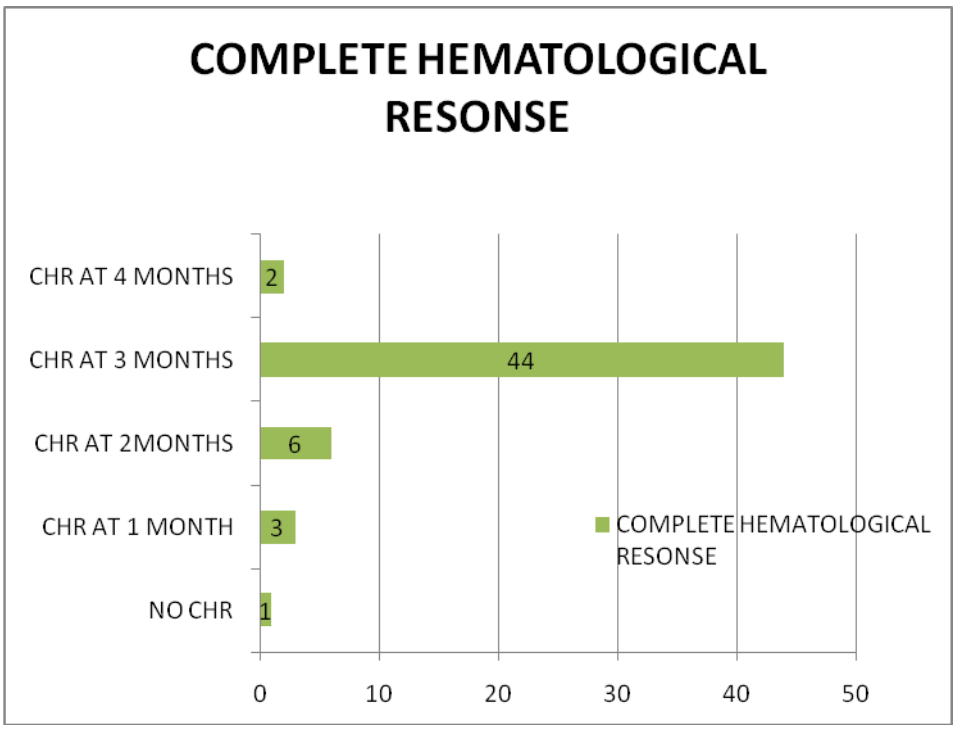
Graph : 1

Dose of Imatinib(mg): 6 patients in pediatric age group were started on Imatinib at a dose of 300 mg/m^2 and rest 51 adult patients were on 400mg.



Graph 2

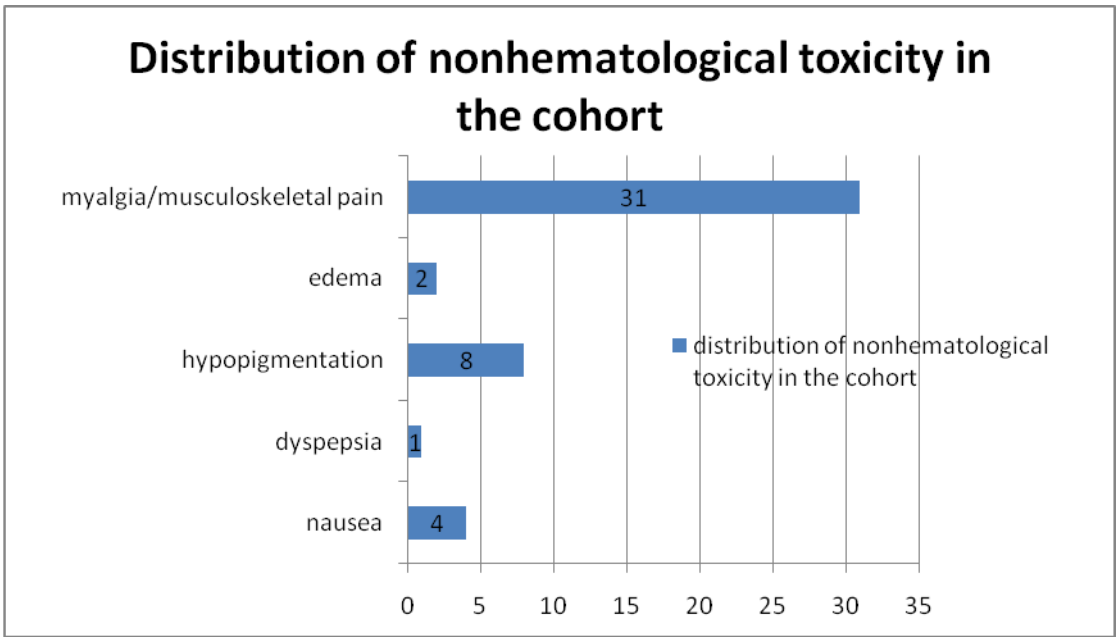
Hematological Response was monitored in patients at initial visits which included the documentation of presence of complete hematological response. 53 (92%) patients achieved Complete hematological response at the end of 3 months and 2 patients with ongoing hematological response attained CHR just after the 3rd month. However, they were continued on same dose of Imatinib.



Graph 3

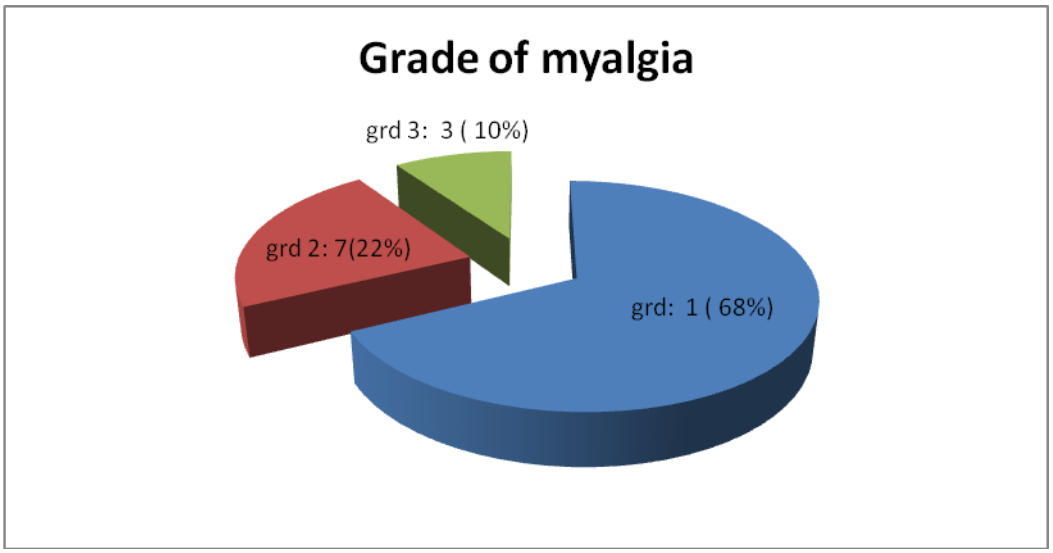
NON HEMATOLOGICAL SIDE EFFECTS

The side effects noted are as stated above. Myalgia and musculoskeletal pain were the most common side effects noted (54%). The next common were hypopigmentation (14%), nausea (7%) and pedal and facial edema which were noted by the patients but resolved over a month without any medication.



Graph 4

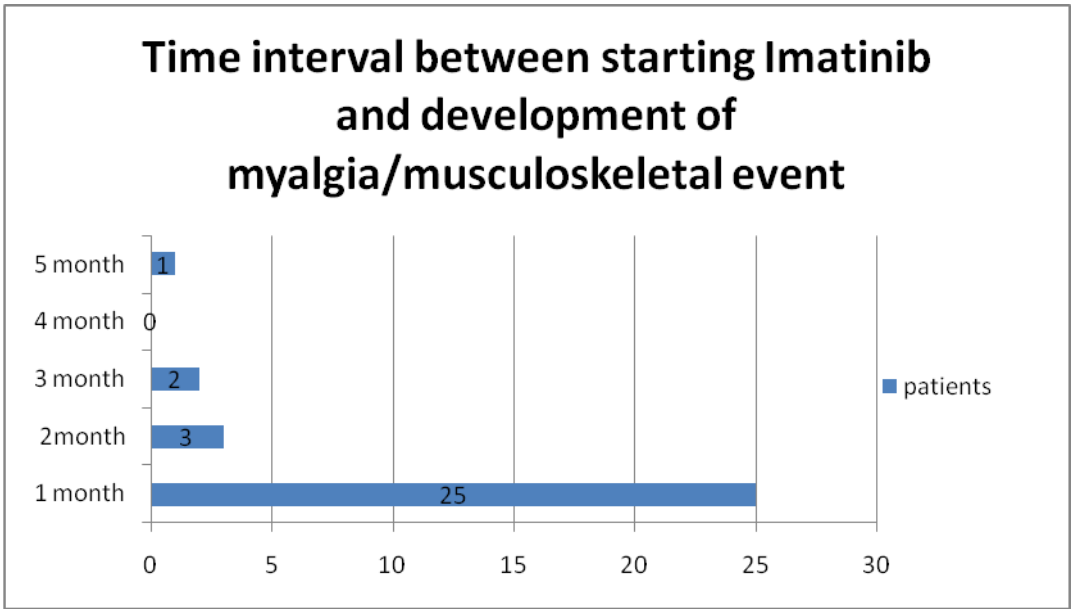
Musculoskeletal events and myalgia



Graph 5

Musculoskeletal pain /myalgia was present in 31 patients (56%), of which 21 (68%) had Grd 1 myalgia and 7 had Grd 2 (22 %) and 3 patients (10%) had grade 3 myalgia.

Time of onset of myalgia /musculoskeletal pain: this event was documented within 1 month in 25 patients (80%), 3 patients had it in 2nd month of starting Imatinib. 1 patient had myalgia in the 5th month.



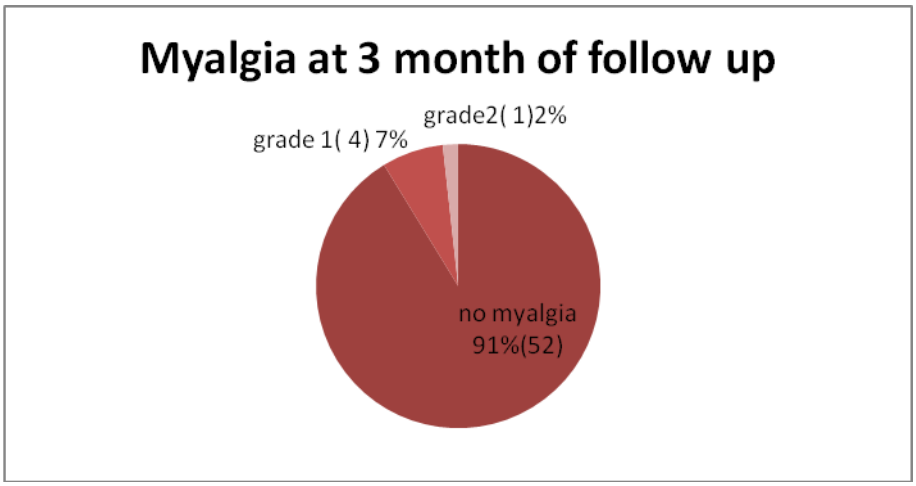
Graph 6

Site of Myalgia- Myalgia was generalized in 30 patients, i.e. they complained of pain in extremities and back pain, there was no diurnal variation observed, 1patient presented with lower back pain.

MYALGIA/MUSCULOSKELETAL PAIN ON 3rd MONTH FOLLOW UP, 52 patients (91%) did not have any myalgia or musculoskeletal pain.

Effect of adding analgesics and calcium supplementation:

Response was present in 29 patients when they were followed on next visit but myalgia persisted in 5 patients although it was grade 1 without any interference in activity of daily living.



Graph 7

Myalgia/musculoskeletal pain on 6th month follow up: Only 1 patient had grade 1 myalgia persisting at 6 monthly follow up (1.7%).

COMPLIANCE ISSUES: 1 patient was non compliant due to myalgia, he had grd 3 myalgia which was present within 1month but resolved with analgesic use.

TREND OF SERUM ELECTROLYTES IN PATIENTS OF CML ON IMATINIB

Table 5

	Mean Serum creatinine mg/dl (+/-SD)	Mean Serum sodium mg/dl (+/-SD)	Mean serum calcium mg/dl(+/-SD)	Mean serum potassium mg/dl (+/-SD)	Mean serum (+/-SD)phosph mg/dl	Mean urine cr (+/-SD)	Mean urine phosphate value (+/-SD)	Mean urine fractional phosphate excretion% (+/-SD)
Baseline (n=57)	0.74(+/-.18)	133.32(+/-3.73)	8.93(+/1.34)	4.17 (+/-.60)	4.32(+/-1.170	53.66(+/36.20)	34.64(+/26.62)	20.82(+/-30.93)
3m value (n=47)	0.80(+/.14)	133.40(+/-2.38)	8.66(+/1.19)	3.85(+/-.47)	3.69(+/-1.04)	50.33(+/43.13)	29.71(+/28.19)	22.61+/-30.14
6m value	0.75	132.62	8.70	3.876	3.557	54.76	49.32	34.89

There is a trend of values being noticed in the following electrolytes

- Mean serum phosphate levels decreased over a period of time. The trend over period of time was not statistically significant when baseline levels were compared with 3rd month level by performing a 2 tailed t test (p value = 0.012). Hypophosphatemia (serum phosphate levels < 2.7 mg/dl) was present in 7 patients at 3rdmonthly evaluation. The phosphate levels at 3 rd and 6 th month was present in 47 and 21 patients respectively.

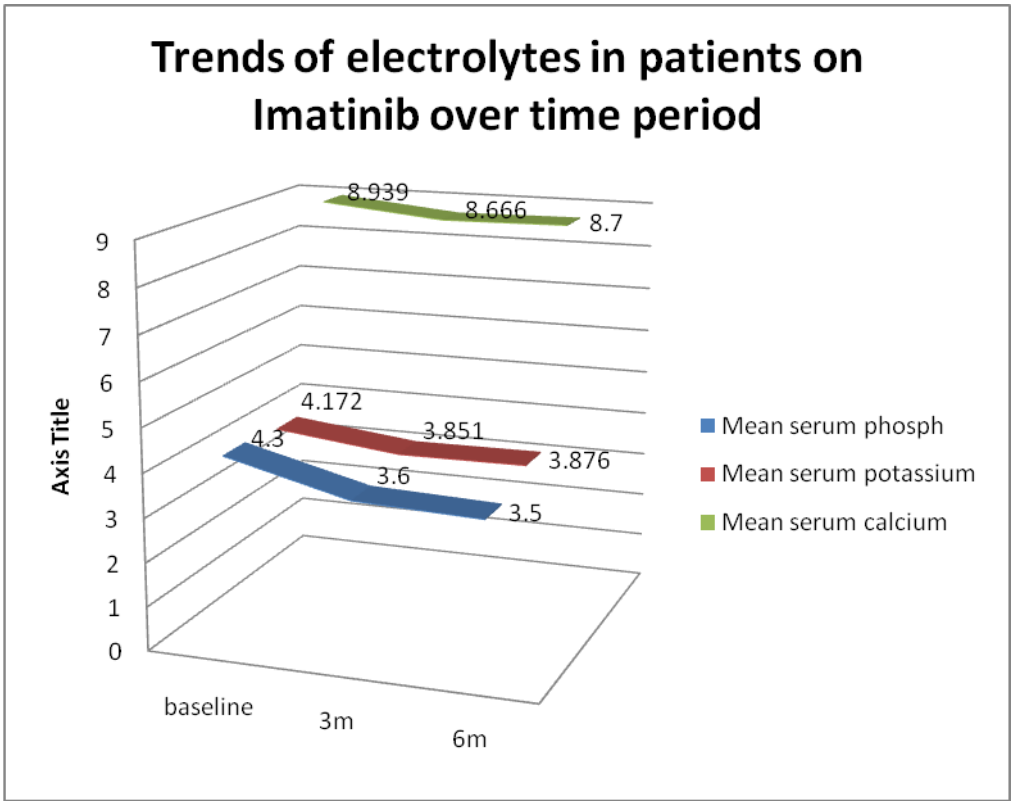
- Likewise increase in urine fractional phosphate excretion was noted but was not statistically significant (p=0.573). This value at baseline could be obtained in 37 patients, in 41 patients at 3 month of follow up and in 21 patients at 6 monthly follow up.

- There was also a trend noted for decrease in mean serum calcium levels although again not statistically significant (p=0.3). There were 28 patients who had levels lower than 8.7 mg/dl at 3 rdmonth, although the serum albumin levels were normal (data for 47 patients present).

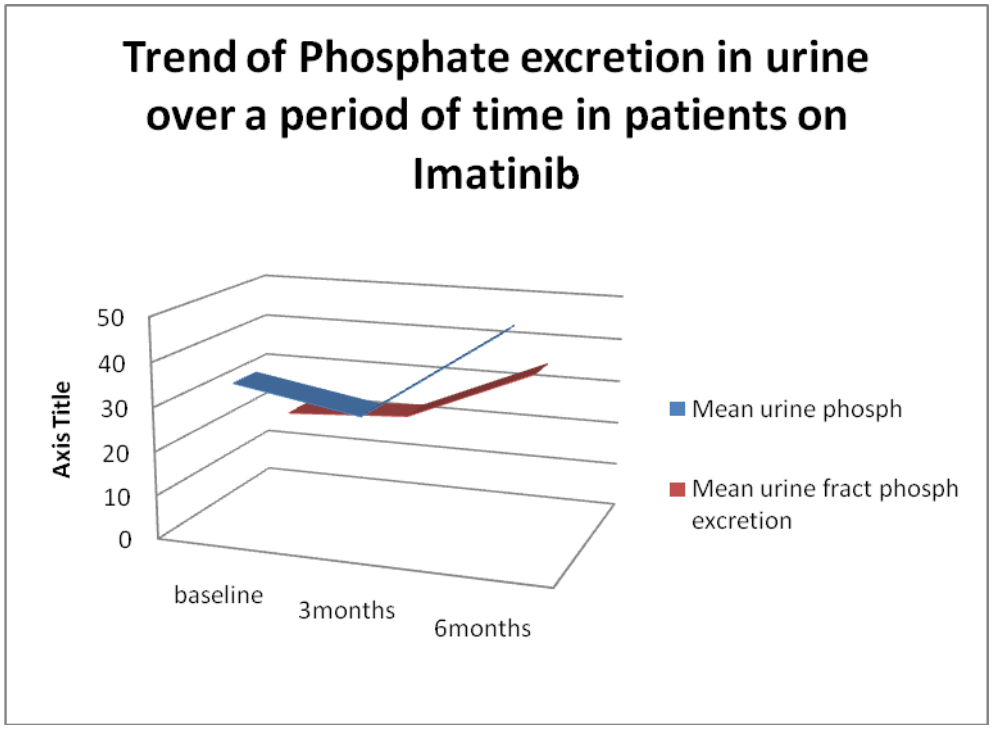
- There was no significant trend noted in mean serum sodium level over a time period neither was any statistical significance noted when baseline levels were compared with 3rdmonthly levels.

- There was a decrease in mean serum potassium levels noted at 3rd month with respect to values but again there was no statistical significance noted.

- To check the validity of the electrolyte tests there was a panel of serum electrolyte and urine tests(for spot phosphate and spot creatinine) was performed taking 10 normal controls. T test was used to check for statistical differencesThere was a statistically significant higher values of serum calcium levels of controls with respect to that of patients on Imatinib(,p value at 3 months 0.005 and at 6 month 0.001).



Graph 8 (above),9 (below)



Myalgia and Musculoskeletal pain and correlation with Electrolyte imbalances when compared at 3rd month.

Table 6

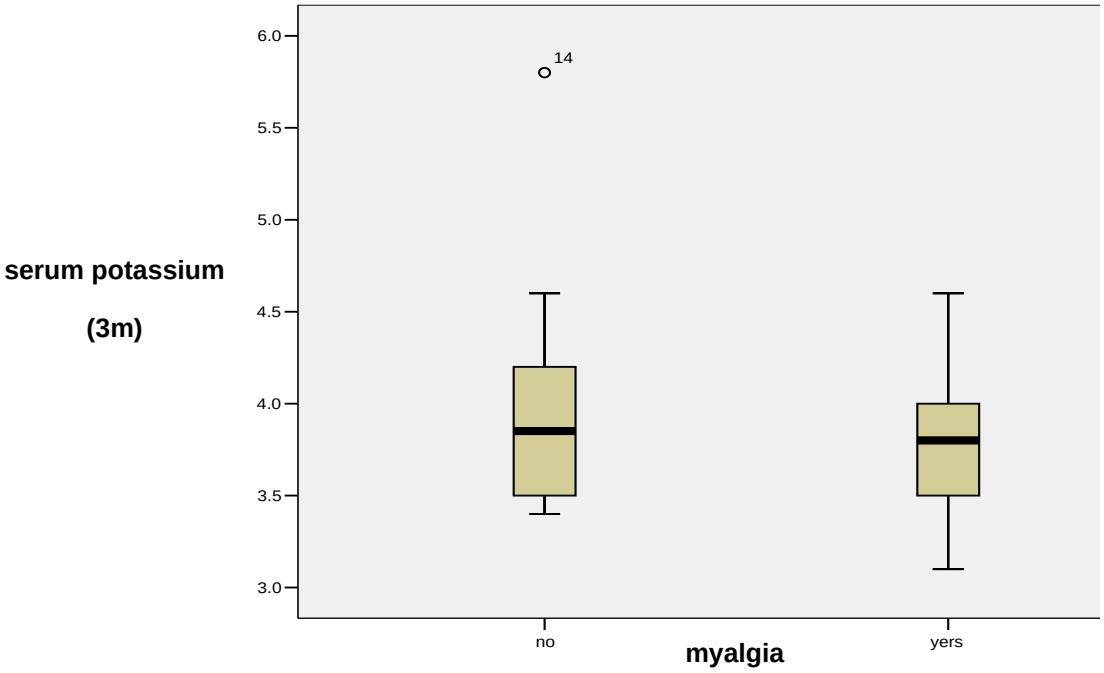
Parameter at 3 m (mg/dl)	Myalgia present N=25	Myalgia absent N=22	P value
Serum phosphate	**3.60**	**3.79**	**0.56**
Serum calcium	**8.6**	**8.7**	**0.71**
Serum potassium	**3.79**	**3.84**	**0.073**

Serum phosphate levels were compared in patients who had a musculoskeletal event versus those who did not have a musculoskeletal event by paired t test .The serum phosphate levels were done in 47 patients at the end of 3rdmonth and these patients were taken into analysis The following was the distribution amongst these 47 patients.

There was no significant differences in the mean values of calcium in patients with and without myalgia at 3rd month.

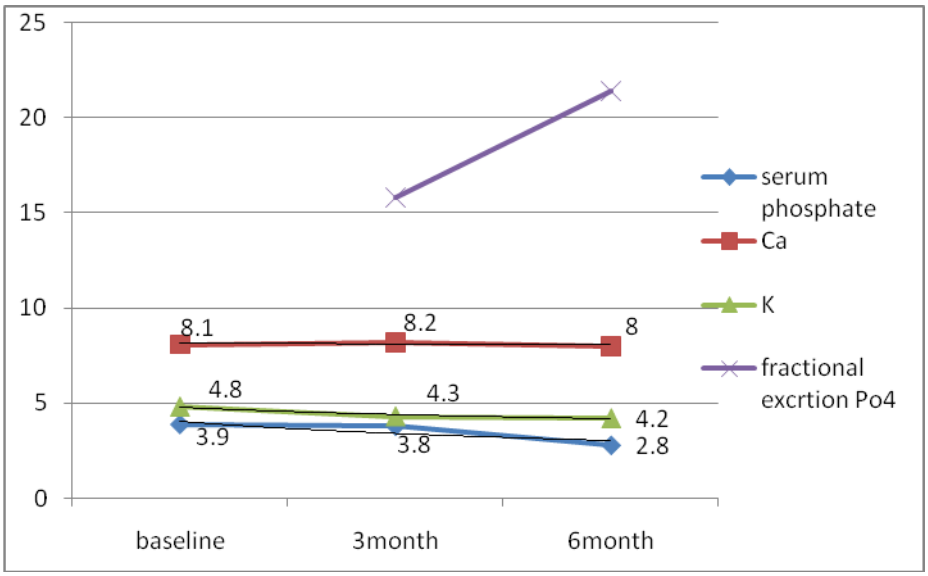
Serum potassium levels were also compared within the cohort of 47 patients at 3 rd month who had myalgia and amongst these patients there was a near significant correlation(p=0.07) between patients who had myalgia and

those with no event i.e. the mean potassium values were lower in patients who had myalgia than in those who did not have it.



Graph 10 patients with relative hypokalemia at 3rd month had more myalgia/musculoskeletal pain when compared to those with higher values

However in 1 patient who had myalgia persisting at the end of 6 months we found the following trend of electrolyte disturbances as previously described a similar trend as seen in the cohort was observed.



Graph 11

Amongst pediatric age group, 1 patient age of 5 years had diminished or no gain in height as a main symptom . After 1 year on Imatinib although he attained CHR within 3 months. He also had low phosphate levels and increase in fractional excretion of phosphate levels.

DISCUSSION

Musculoskeletal pain and myalgia are accounting for *significant* nonhematological toxicity in patients who are started on Imatinib as shown in our study as well as in previous clinical trials on Imatinib, including IRIS study.

- **Myalgia/Musculoskelatal toxicity incidence reported**

Table 7

Studies looking at incidence of myalgia	**Patients on Imatinib**	**Musculoskeletal Pain& myalgia (all grades)**	**Median dose of Imatinib**
IRIS trial[20](newly diagnosed CML patients included)	551	38.3% & 21% (Grd 3/ 4 =2.7, 1.5%)	400 mg
Phase 1 trial for Imatinib[19]	83	43%	Dose range from 25 mg - 1000mg(median not specified)

Our study	57	54% (Grd 3 toxicity 1% , Grd 4 not present)	400 mg

In IRIS study they have reported myalgia and musculoskeletal pain separately, but it was not so reported in the phase 1 trial of Imatinib, we have not analyzed this separately. As the hypothesis given by Berman et al [29]is same for both these side effects and the phase 1 trial for Imatinib too did not report it separately; we considered it as one side effect. The incidence of our grade 3 toxicities are same as that found in IRIS trial although we did not observe any Grade 4 toxicity in our patients. As reported in literature[23] most of the patients report this side effect within 1 month of starting Imainib, we also found that nearly 80% of our patients had this as a side effect in first month of therapy.

Trend of Serum Electrolytes in patients who are on Imatinib and correlation with Myalgia/ Musculoskeletal pain.

Serum and urinary phosphate levels in patients in Imatinib

The most common electrolyte imbalance reported in literature is *decrease in phosphate levels*[30,34] and this is associated with altered bone mineral metabolism.[29]

Table 8:

Studies as in literature	**Serum Phosphate (mean value+/- SD) at following months**				**FRACTIONAL EXCRETION OF PHOSPHATE%**			**Correlation between phosphate imbalance and myalgia/ musculoskeletal pain**
	0m	**3m**	**6m**	**12m**	**0**	**3m**	**6m**	
Susannah O'Sullivan et al[31](CML patients: prospective study)	Observed a fall in serum Phosphate levels between 0-3months but stabilized after that (n=9)				Phosphaturia increased between baseline and 18months			Not studied
Osorio et al[32] (CML patients :prospective study)	3.7 (+/- 0.6) n=36)	2.98 (+/- 0.66) (n=36)	3.02 (+/- 0.48) (n=34)	2.84 (+/- 0.5) (n=27)	The median value at 12 months was 77.5% (range, 49–83) (normal value > 79%).			No correlation found
Our study (N=57) (CML patients: prospective study)	4.3 +/- 1.17 (n= 56)	3.69+/- 1.0 (n=46)	3.5 +/-0.6 (n= 21)	X NA	20 (+/- 5.5) (n=37)	22.6(+/- 30.14) (n=41)	34.89 (+/-51) (n=21)	No correlation found p=0.56

Osorio et al tried to correlate the musculoskeletal events with serum phosphate. They found that decrease in phosphate levels occur and found a level below 2.5 mg/dl in 14 patients over follow up. Their follow up period was 12 months and they found persistent decrease in phosphate levels unlike the study by Sussanah O'Sullivan who observed a fall in serum phosphate levels over the first 3 months but thereafter no fall in serum phosphate was noticed. Both the authors confirmed the hypothesis that there is secondary hyperparathyroidism as PTH levels were increased on follow up studies. We also found an increase in phosphaturia over a period of time and this coupled with our finding of hypocalcemia supports the hypothesis by Berman et al that there could be a possibility of secondary hyperparathyroidism present during intake of Imatinib, though we could not carry out serum PTH studies because of financial constraints.

Another possibility of hypophosphatemia caused by Imatinib given by Osorio et al was that it is acting on the c-kit cells of renal tubules; however they did not measure other parameters of renal glycosuria which could be caused by Fanconi syndrome as proposed by Helene Francois et al. However, this hypothesis has been rejected by Kate Vandyke et al in his review article stating that this mechanism is only stated in case reports and is not a consistent observation.

Serum calcium levels in patients on Imatinib: Decreased levels of serum calcium have been described by Berman et al[29] and by Kate Vandyke et al[17] as a primary event which triggers PTH levels which in turn cause hypophosphatemia. This hypocalcemia is caused by decreased bone turnover due to inhibition of resorption activity of osteoclasts by Imatinib. The serum calcium levels observed and their correlation with myalgia in various studies were as follows:**Table 9**

	Serum Calcium levels over a time period of 0, 3, 6months(mg/dl)			**Correlation with myalgia**
Osorio et al[32] 36 patients studied prospectively	Reported diminished levels over time: 0.38+/- 0.08(3m), 0.45 +/- 0.09 (6m) and 0.37+/- 0.08 mg/dl(12m)			No correlation observed
Zekri at al[32] 16 patients on adjuvant Imatinib for GIST	At the start of Imatinib treatment, all patients had normal serum calcium levels (mean 9.8 ± SD 0.44 mg/dl). All patients exhibited a rapid and sustained fall in adjusted serum calcium during treatment with Imatinib to 9.2 ±0.30 mg/dl at 6 months			Proposed a correlation that relative hypocalcemia may cause hypexcitability at neuromuscular junction and can cause myalgia and cramps based on a index case, however failed to establish any significant correlation
Susannah O'Sullivan et al	change from baseline -0.3 (-0.5, -0.1) mg/dl p <0.05			Not studied
Our study	0 month	3month	6month	No correlation observed p value= 0.71
	8.9+/- 1.3 (n=57)	8.6+/-4.0 (n=46)	8.7+/- 3.8(n=21)	

Although the studies looking at calcium metabolism were showing a decreased trend of calcium, there was no frank hypocalcemia. Likewise, we also never got any patient with calcium levels less than 7.0 mg /dl. We have at least one value for serum albumin for most of the patients unlike the above studies which have looked stringently into the ionized calcium levels for patients at every visit. The observations of Zekri et al that relative hypocalcemia may be the cause of myalgia/ musculoskeletal pain were initially based on an index case of GIST on adjuvant Imatinib who had hypocalcemia and severe myalgia and on stopping Imatinib both resolved. They further studied this prospectively in 16 patients and found that there was significant reduction in calcium values at 6 months when compared with baseline. This study highlights the important aspect that the electrolyte imbalance and probably myalgia is not dependent on the underlying disease but is being caused by the drug and that it can be reversed once the drug is stopped.

Imbalances of Potassium and association with musculoskeletal pain and myalgia:

Imbalances of serum potassium have not been explained in literature in patients who are on Imatinib. In our patients, the mean potassium levels at 3 months were lesser than compared with baseline values (baseline value of 4.20 and 3 rd month potassium value of 3.85, *p* value =0.57). However the there was

a trend towards association of myalgia in patients who had low potassium levels (p=0.07). This finding may have been probably more significant with more patients in the study and further follow up and this finding could support renal tubular dysfunction effect of Imatinib.

Compliance issues and Myalgia and Musculoskeletal pain:

In our study we found only 1 patient to be non compliant due to myalgia. This patient was started on Imatinib and had grade 3 pain. Imatinib had to be stopped for the same and his pain was relieved by NSAIDs. He had decreased phosphate levels from baseline but not in range of hypophosphatemia.

Pediatric CML and Imatinib: Pediatric CML accounts for nearly 3% of pediatric leukemias.Imatinib has now nearly replaced allogenic stem cell transplant as a first line option in pediatric patients. However the data regarding long term effects in the treated pediatric patients is awaited. One of the toxicities is that of decreased linear growth in prepubertal age in patients on Imatinib. We also in our study had one patient 5 years of age in our study for whom the father complained of no increase in height nearly after a year of being started on Imatinib. This again throws light on the Serum electrolyte imbalances due to decreased bone resorption.[33,35]

CONCLUSION

This study highlights the following factors:

- *Myalgia and musculoskeletal is the one of the common nonhematological side effect in patients of chronic myeloid leukemia who are initiated on imatinib. In our study it was the most common one.*

- *Generalized myalgia and bone pains is the most common presentation in a patient who is started on Imatinib, this is usually a Grd1/2 pain and it usually presents in the first month of starting Imatinib and the response to NSAIDs alone or with calcium supplementation is good (91%).*

- *There is a trend for decrease in Serum Calcium, and Phosphate levels as earlier reported in literature. Since there is increase in Fractional excretion of phosphate, considering this the most common etiology could be secondary hyperparathyroidism,although we did not look for serum Parathyroid levels in our study. This trend of decrease in electrolyte levels continues even after the myalgia and musculoskeletal pain is relieved , we found the trend even at 6 months.This is especially important for calcium where the difference in 6 monthly values was quite significantly low when compared to our normal controls.*

- *However we could not find a statistical significance of myalgia and musculoskeletal pain in patients who had relative hypophosphatemia and hypocalcemia, probably because of a small sample size but nonetheless this probably high lights the importance of measuring the serum electrolyte levels and bone mineral density especially in a pediatric and elderly age group who are on Imatinib where altered bone metabolism can make an impact on genral health.*

- *We found a near statsical significance(p=0.07) in patients having myalgia and those with low potassium values. There is not much evidence for this finding except for case reports, further studies are required to confirm this finding.*

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Proforma: *Prospective evaluation of myalgia& musculoskeletal pain in patients of CML –chronic phase treated with Imatinib AND possible corelation with electrolyte imbalances-*

BASELINE EVALUATION

Pt: Name Age Sex

UHID CIndex

Tel No.

HISTORY OF MUSCULOSKELETAL DISORDER Y / N

DRUG INTAKE (PLEASE SPECIFY) _____

Imatinib starting Date_____

- **Responses disease at**
    - **3m**
    - **6m**
- **Side effects of Imatinib(other than myalgia)**
- **Compliance issue due to side effects**
- **Compliance issue related to musculoskeletal event(y/N)**
    - **Myalgia/ Musculoskeletal pain (y/N)**
    - **Grd**
    - **Duration(months)**
    - **Effect of adding analgesics (grd) &Effect of Calcium supplementation (grd)**

At Follow Up

	Myalgia Grd	**Respone Of disease**	***Cr***	***Na+***	***Ca2+***	***K +***	***PO4+***	***Urine spot Creatinine***	***Urine spot PO4***	**Serum Albumin**
At baseline										
At 3m										
At 6 m										

CTC grade 2.0

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

ABBREVIATIONS

- ***CML**: Chronic myeloid leukemia*
- ***Ph chromosome** : Philadelphia chromosome*
- ***CCyR:** Complete Cytogenetic response*
- ***GIPAP**: Glivec International Patient Assisted Programme*
- ***NSAIDs:** Non Steroidal anti Inflammatory Drug*
- ***Ca^{2+}:** serum calcium /ionized Calcium*
- ***K^{+}:** Serum Potassium*
- ***PO_4** : Serum Phosphate*
- ***Na +:** Serum Sodium*